REMARKS

These remarks are in response to the Office Action mailed February 25, 2005.

Claims 1 and 19 have been amended. Claims 11-13 have been previously withdrawn. Amendment to claims 1 and 19 are supported in the specification. Hence, no new matter has been added and claims 1-10 and 13-29 are pending in this application. Entry of the amendment is respectfully requested.

I. Amendments to the claims

Claims 1 and 19 have been amended to claim the subject matter of the invention with greater particularity and specificity. The amendments are fully supported in the application as filed.

Examples 11-16 describe "therapeutically effective" mucociliary clearance amounts. Therefore, amendment of claims 1 and 19 do not present new matter and are fully supported by the specification.

II. Rejection Under 35 U.S.C. §102(e)

Claims 1-10, 14 and 16-18 are rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 6,583,108 to Tamburini et al. (hereinafter, "Tamburini"). Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either *expressly or inherently* described, in a single prior art reference (*emphasis added*). *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, missing elements cannot be supplied by the knowledge of one skilled in the art or the disclosure of another reference in order to give rise to an anticipation rejection. *Structural Rubber Products Co. v. Park Rubber Co.,* 749 F.2d 707, 223 USPQ 1264 (Fed. Cir. 1984).

According to the Office Action, claims 1-10, 14 and 16-29 are under consideration as they pertain to human bikunin, or SEQ ID NO:52 (see the top of page 2 of the Office Action) and its use for treatment of adult respiratory distress syndrome (ARDS) and emphysema (column 15, lines 6-11 and 14-16; and column 18, last sentence). However, as will be discussed in more detail below, Tamburini does not disclose, either *expressly or inherently,* "each and every element" of the claimed invention.

Examples 11-16 of the present application (pages 62-67) are not disclosed or described in Tamburini, which only discloses Examples 1-10 relating to isolation, characterization and identification of protease inhibitor functions of human placental bikunin. Although, Tamburini discloses human placental bikunin sequences and fragments thereof, Tamburini does not provide any suggestion or examples indicating that the sequences and fragments thereof are capable of increasing mucociliary clearance (MCC).

Further, in the instant application as filed, Applicants disclose the use of human placental bikunin and fragments thereof to increase MCC in mucociliary dysfunction diseases. This is distinct from a course of treatment that would be selected to treat ARDS. ARDS is respiratory failure due to a rapid accumulation of fluid in the lungs from breakdown in the permeability of the endothelial membrane of the capillaries and the alveolar membrane of the air sacs in the lungs. When the air sacs in the lungs collapse or fill up with fluid, the lungs do no ventilate air properly and become stiff; hence another term for ARDS is "stiff lung." ARDS is not a specific disease *per se*, rather it is a response to acute injury of the lungs caused by various conditions (e.g. inhalation of smoke or toxic fumes, widespread infection, e.g., bilateral pneumonia, sepsis, near-drowning, a major blood loss, shock, direct trauma to the chest, and the like). In short, ARDS is <u>not</u> a condition characterized by an accumulation of mucus (see Exhibit A containing an abstracts and descriptions of ARDS from DrCoop.com and WEBMD.com), and therefore would not be treated by administration of human placental bikunin of the invention. Thus, Tamburini's disclosure that human placental bikunin and fragments thereof can be used to treat ARDS cannot anticipate the claimed invention, since mucus accumulation is not symptomatic of ARDS. In contrast, the claimed invention methods use human placental bikunin and fragments thereof to *increase the rate of mucociliary clearance.* Therefore, the methods of the claimed invention aim to treat those diseases whereby there is an accumulation of mucus, e.g. cystic fibrosis and not such diseases such as ARDS.

Further, often diseases typified by mucociliary clearance dysfunction, e.g., cystic fibrosis have impaired anion secretion and Na^+ absorption in the airways (increased intracellular Na^+

absorption). Inhibition of Na^+ transport using human placental bikunin and fragments thereof is described in Examples 11 and 13. Example 11 describes the inhibition of the potential difference across the sodium channel *in vivo* in guinea pig trachea (page 62-63; FIG. 15), and Example 13 describes the inhibition of the amiloride-sensitive short circuit current *in vitro* in HBE cells (page 67; FIG. 20). In subjects with mucociliary dysfunction, the accumulation of a viscous mucus (or less hydrated mucus) on the surface of the epithelial cells occurs due to the high intracellular Na^+ concentration and the subsequent movement of water down its concentration gradient into the cell. Bikunin is believed to inhibit sodium transport (reducing the intracellular Na^+ concentration), thereby blocking water moving down its concentration gradient and into the cell. Additional extracellular water hydrates the mucus residing on the surface of the epithelium. The increased hydration of the mucus allows for increased mucus clearance by the ciliary apparatus on the apical side of the epithelium, in other words increasing "mucociliary clearance." It would be anticipated that the additional hydration of the airways might exacerbate rather than ameliorate the condition of ARDS. Examples 11 and 13 show that human placental bikunin can inhibit the sodium current.

Moreover, Example 12 confirms that human placental bikunin inhibiting the sodium current has an effect on the rate of mucociliary clearance based on measurements of increased levels of tracheal mucus velocity (or TMV) *in vivo* in guinea pig tracheal is observed (page 63-64; FIG. 16(c). Figure 16(c) shows that human placental bikunin increases TMV *in vivo* in guinea pig tracheal relative to saline over a sustained period of 1.5 to 2.5 hours post-administration of the bikunin. Thus, Example 12 supports the results described in Examples 11 and 13, that the claimed bikunin proteins and fragments thereof increase mucociliary clearance by inhibiting the sodium current and reducing the intracellular accumulation of Na^+ thereby hydrating the mucus on the surface of the epithelium. Increased hydration of the mucus means a less viscous mucus has a increased rate of expectoration or "clearance" as observed by measurement of TMV.

The results of Examples 11, 12 and 13 are further supported in a post-filing journal article by Bridges et al., "Na^+ transport in normal and CF human bronchial epithelial cells is

inhibited by BAY 39-9437," *Am. J. Physiol Lung Cell Mol Physiol* 281: L16-L23, 2001. Bridges et al. is attached as Exhibit B. Bay 39-9437 is "an 170 amino-acid human serine protease inhibitor (page L17, left hand column)," and corresponds to SEQ ID NO:52 (1-170) of the claimed invention.

Thus, based on the foregoing discussion, Applicants submit that Tamburini does not anticipate the claimed invention because Tamburini does not disclose or even suggest *any* method for mucociliary clearance. That is, absent any direct (express) or even indirect (inherent) teachings, a method of using "a therapeutically effective mucociliary clearance stimulatory amount of a composition comprising a substantially purified human serine protease inhibitor protein containing at least one Kunitz-like domain" cannot be supplied by the knowledge of one skilled in the art. *Structural Rubber Products Co. v. Park Rubber Co.,* 749 F.2d 707, 223 USPQ 1264 (Fed. Cir. 1984). One skilled in the art would not be able to infer from Tamburini that bikunin increases MCC.

Accordingly, withdrawal of the rejection of claims 1-10, 14 and 16-18 under 35 U.S.C. § 102(e) is respectfully requested.

III. Rejections Under 35 U.S.C. § 103(a)

Claims 1-10, 14 and 16-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Delaria et al. in view of Rasche et al, Fritz et al., and O'Riordan et al. (hereinafter, "Delaria," "Rasche," "Fritz," and "O'Riordan," respectively). Applicants respectfully traverse this rejection.

To establish *prima facie* obviousness of a claimed invention, all the claim limitation must be taught or suggested by the prior art. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Further, if an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine,* 837 F.2d 1071, 5 USPQ 1596 (Fed. Cir. 1988). MPEP 2143.03.

Briefly, Delaria discloses bikunin (1-170), a serine protease inhibitor; Rasche discloses that aprotinin/Trysalol® increases expectoration and liquifaction of mucus to improve lung function, for example, in those subjects with chronic obstructive bronchitis; Fritz discloses various modified Kunitz-type inhibitors; and O'Riordan discloses that treatment with an inhibitor of neutrophil elastase increases mucociliary clearance.

However, the cited references combined do not disclose or suggest that human placental bikunin increases mucociliary clearance. O'Riordan discloses that ICI 200,355 (10 mg), a *specific* inhibitor of neutrophil elastase, increases the rate of mucociliary clearance or tracheal mucous velocity (TMV). Yet, there is no disclosure or suggestion in any of the other cited references which would motivate one skilled in the art to use human placental bikunin, a *non-specific* inhibitor of various serine proteases, including neutrophil elastase, to increase mucociliary clearance. Although Delaria discloses bikunin 1-170, Delaria does not disclose or suggest that bikunin 1-170 is involved in treatment of any diseases or that it may increase mucociliary clearance. This fact was noted by the Office in the Office Action mailed December 27, 2002 (page 7). Further, Rasche and Fritz do not cure the deficiencies of either Delaria or O'Riordan, alone or combined, because there is no suggestion to motivate one skilled in the art to take the disclosures of either Fritz or Rasche and combine it with Delaria and O'Riordan. Moreover, the concentration used in O'Riordan is at least 3 orders of a magnitude greater than that disclosed in the present application (see Examples 11-13, pages 65, whereby at least 5ug was effective to increase mucociliary clearance). At best, in view of these disclosures, one skilled in the art might find it *obvious to try* the combination of cited references, however, *obvious to try* is not the standard under 35 U.S.C. § 103. *In re Geiger,* 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987).

Thus, based on the foregoing discussion above, it cannot be said that the combination of Delaria in view of Rasche, Fritz and O'Riordan discloses:

> A method for accelerating the rate of mucociliary clearance in a subject with mucociliary dysfunction comprising administering to the subject a therapeutically effective mucociliary clearance stimulatory amount of a composition comprising a substantially purified human serine protease inhibitor protein containing at least one Kunitz-like domain.

Further, based on the forgoing discussion, one skilled in the art would not be motivated to take the disclosures of the cited references to produce the claimed invention because the claimed invention is not clearly described nor suggested in the cited references. None of the references describe the effect of intracellular accumulation of Na^+ leading to increased mucus viscosity, such that inhibiting intracellular Na^+ transport would increase hydration to the mucus and facilitate increased mucociliary clearance as evidenced by increased tracheal mucus velocity (TMV). Therefore, the cited references, alone or in combination, cannot render the claimed invention obvious because not all the claim limitations are disclosed or even suggested.

Accordingly, withdrawal of the rejection of claims 1-10, 14 and 16-29 under 35 U.S.C. § 103(a) is respectfully requested.

IV. Conclusion

Applicants submit that the pending claims are in condition for allowance. Reexamination, reconsideration, withdrawal of the rejections, and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged to contact the undersigned below.

No fee is believed due in connection with this Amendment. If any additional fees are due, the Commissioner is hereby authorized to charge any fees that may be required by this paper to Deposit Account No. 07-1896. A duplicate copy of this Transmittal Sheet is attached.

Respectfully submitted,

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